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Editorial

Synthesis and Biological Activity of Novel Complexes with Anthranilic Acid and Its Analogues

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Anthranilic acid analogues and their derivatives hold significant therapeutic potential for crafting designed compounds aimed at regulating cancer-causing pathways and addressing metabolic challenges linked to diabetes, antiviral agents [1], and biologically tolerant anti-inflammatory compounds [2,3]. Anthranilic acid-based derivatives also have anticoagulant, antiallergic, antipyretic, diuretic, analgesic properties. Anthranilic acid serves as a precursor for crafting numerous commercial drugs and pharmaceuticals, playing a pivotal role as the foundational framework in various drug categories like fenamates and NSAIDs. Anthranilic acids and their derivatives have interesting antimicrobial, antiviral and insecticidal activities.

Furthermore, the analogs of anthranilic acid and their derivatives act as initiators of apoptosis, suppressors of the hedgehog signaling pathway, blockers of the mitogen-activated protein kinase pathway, and inhibitors of aldo-keto reductase enzymes.

Similarly, their antiviral characteristics emerge through the inhibition of HCV NS5B polymerase, while they exhibit antibacterial efficacy by blocking the UppS pathway. Additionally, anthranilic acid-derived α-glycosidase inhibitors play a substantial role in diabetes management. The derivatives of anthranilic acid find applications in neuroprotection by downregulating pivotal pathways accountable for the expression of neuropathological traits and neurodegeneration.

However, the transition metal compounds of anthranilic acid derivatives provide therapeutic possibilities in diabetes mellitus and obesity through the control of α-glucosidase activity.

Recently, Chuanfeng Niu et al. synthesized novel complexes using trifluorinated anthranilic acid derivatives [4]. The complexes' cytotoxic effects on A549 (human lung cancer cells) and Hela (human cervical cancer cells) were also investigated. Structural analysis through single-crystal X-ray crystallography revealed that all three complexes exhibit penta- or six-coordination of Co and Zn atoms, adopting a configuration of a twisted square pyramid or a triangular bi-conical geometry.

A novel ligand [N-(4-chlorobenzoylamino)-thioxomethyl]anthranilic acid (CBA) was synthesized [5]. Numerous metal complexes of CBA with Mn, Co, Ni, Cu, Pd, Zn, Cd and Hg were obtained.

New metal complexes of N-phenyl anthranilic acid were obtained with copper, nickel, and cobalt [6]. The ligand and its resulting complexes were subjected to testing against various bacterial species including *Shigella sonnei*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Salmonella typhi*, and *Proteus mirabilis*, as well as *fungal species* such as *Curvularia lunata*, *Aspergillus niger*, *Alternaria solani*, *Bipolaris* spp., and *Aspergillus fumigatus*. The results of the antimicrobial assessments suggest that the complexes exhibit higher activity compared to the ligand itself.

A series of nano-sized anthranilic acid metal complexes were successfully synthesized and characterized, involving metals like Zn(II), Bi(III), Fe(II), Co(II), Cu(II), Mn(II), Al(III), Ni(II), and Cr(III) [7]. Additionally, their potential catalytic role in the reduction in

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4-nitrophenol was investigated. These complexes, along with the free ligand, were subjected to testing against various plant pathogens encompassing bacteria, fungi, and nematodes. The metal complex with silver showed good antibacterial, antifungal and nematocidal activities.

Raza et al. documented the synthesis of ligands derived from anthranilic acid and phthalic anhydride, along with their corresponding metal complexes involving Cd(II), Co(II), Pb(II), and Cu(II) [8]. Furthermore, they assessed the antibacterial properties of these compounds.

Ahmad Aziz et al. successfully synthesized a new Schiff base through the reaction of piperonal and anthranilic acid [9]. They then prepared novel complexes involving Cu(II), Ni(II), Pb(II), Sn(II), and Mn(II) with this Schiff base. The resulting compounds were subjected to testing for both antibacterial and antioxidant activities.

Zheng and Ma reported that metal complexes derived from anthranilic acid derivatives represent a novel category of non-competitive inhibitors for α-glucosidase [10]. Their in vitro analysis indicated a notably improved biological profile for the complexes when compared to both the free ligands and the metal ions themselves. Among these complexes, those containing Ag(I) exhibited the most remarkable inhibition of α-glucosidase activity, showcasing a 4000-fold increase in potency compared to the free ligands.

Recently, novel mixed-ligand dinuclear metal(II) complexes, consisting of nthranilic acid and pyridine-2-aldoxime, were obtained with Mn(II), Ni(II), Co(II), Cu(II), Zn(II), and Cd(II) [11]. All of these metal complexes were subject to assessment against various microbial strains. Notably, the Cd(II) complex exhibited promising inhibitory activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*.

In a related study, six mixed-ligand complexes involving anthranilic acid, leucine, and monochloroacetic acid with copper, nickel, and cobalt were synthesized [12].

In their study, L. A. Karem et al. presented the spectroscopic, structural, and antibacterial characteristics of mixed ligand complexes formed using a Schiff base along with anthranilic acid [13]. The research involved evaluating these compounds against two categories of bacteria: Gram-positive and Gram-negative strains. Kamal Rashid Hsejan Al-Jorani investigated a study where several mixed-ligand complexes incorporating Co(II), Ni(II), Cu(II), and Zn(II), along with anthranilic acid and 2-(1H-benzimidazol-2-yl)aniline derivatives, were synthesized and characterized [14]. The results indicated that the complexes exhibit an octahedral geometry with the presence of two water molecules. In the PhD thesis of S. Doungsoongnuen in 2011, mixed-ligand complexes with Cu(II), Ni(II), Zn(II), Mn(II) from sulfonamides of antranilic acid and 2,3,4-aminopyridines [15] were reported.

Anthranilic acid readily undergoes reactions with W(VI) oxo or organoimido tetrachlorides, resulting in the formation of complexes with the following structure: $[W(X)Cl_3(HO_2C\ C_6H_4NH\text{-}2)]$ [X = O (1), NPh (2)] [16]. The chelating ligand derived from anthranilic acid coordinates in an acid/amide form. Comparative structural analysis has been conducted, drawing parallels between related complexes involving salicylic acid.

T. G. Ros et al. presented a study involving the immobilization of the rhodium/anthranilic acid complex onto fishbone carbon nanofibers [17].

S. Ozkan et al. reported the synthesis and analgesic activity of hydrazides derived from 2-phenoxybenzoic acid and N-phenyl anthranilic acid [18]. Additionally, they explored the oxidative polymerization of N-phenyl anthranilic acid within a heterophase system.

Tatsuaki Matsubara et al. focused on the synthesis of anthranilic acid derivatives [19]. They achieved this through an iron-catalyzed ortho amination process involving aromatic carboxamides and N-chloroamines.

Recently, Prasher and Sharma presented a mini-review exploring the medicinal chemistry of anthranilic acid derivatives [20].

In conclusion, we have summarized that the anthranilic acid and their derivatives and various metal complexes have interesting antimicrobial activities [6–13], cytotoxic [4], anti-inflammatory properties [2,3] and are the inhibitors of aldo-keto reductase enzymes [21].

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References

1. Wang, Y.; Xu, F.; Luo, D.; Guo, S.; He, F.; Dai, A.; Song, B.; Wu, J. Synthesis of anthranilic diamide derivatives containing moieties of trifluoromethylpyridine and hydrazone as potential anti-viral agents for plants. *J. Agric. Food Chem.* **2019**, *67*, 13344–13352. [CrossRef] [PubMed]
2. Prasher, P.; Mudila, H.; Sharma, M.; Khati, B. Developmental perspectives of the drugs targeting enzymeinstigated inflammation: A mini review. *Med. Chem. Res.* **2019**, *28*, 417–449. [CrossRef]
3. Singh, P.; Prasher, P.; Dhillon, P.; Bhatti, R. Indole Based Peptidomimetics as Anti-inflammatory and Anti-Hyperalgesic Agents: Dual Inhibition of 5-LOX and COX-2 Enzymes. *Eur. J. Med. Chem.* **2015**, *97*, 104–123. [CrossRef] [PubMed]
4. Niu, C.; Zong, Z.; Zhang, X.; Wu, R.; Li, N.; Wang, H.; Bi, C.; Fan, Y. Synthesis, structures and biological activity of novel complexes with trifluorinated anthranilic acid derivatives. *J. Mol. Struct.* **2019**, *1194*, 42–47. [CrossRef]
5. Basima, M.S.; Murtadha, A.F. Synthesis and Characterization of Some New Metals Complexes of [N-(4-chlorobenzoyl amino)-thioxomethyl] Anthranilic Acid (CBA). *AL-Qadisiyha J. Sci.* **2014**, *19*, 150–165.
6. Rajalakshmi, R.T.; Bheeter, S.R.; Vasanth, N. Synthesis and Characterisaion of Biologically Active Metal Complexes of N-Phenyl Anthranilic Acid. *ReTeLL Res. Teach. Learn. Lett. Inter-Discip. Ref. Res. J.* **2015**, *15*, 30–37.
7. Nawaz, M.; Abbasi, M.W.; Tariq, M.; Graham, J.P.; Al-Hagri, A.-R.S.; Elkarim, A.A.; Mohamed, M.E.; Nissapatorn, V.; Taha, M.; Hisaindee, S. Synthesis of metal anthranilate complexes: Catalytic and antipathogenic studies. *BMC Chem.* **2022**, *16*, 21. [CrossRef] [PubMed]
8. Raza, S.; Iqbal, Y.; Hussian, I.; Raza, M.; Shah, S.U.A.; Khan, A.; Taj, R.; Rauf, A. Synthesis of Anthranilic Acid and Phthalic Anhydride Ligand and their Metal Complexes. *Biochem. Anal. Biochem.* **2013**, *2*, 1009–2161. [CrossRef]
9. Ahmad, A.; Abid, O.U.R.; Rehman, W.; Kashif, M.; Zaman, R.; Ali, M.; Mir, S.; Qureshi, M.T. Ultrasonic Assisted Synthesis, Characterization and Bioactivity Assessment of Novel Piperonal Based Schiff Base and Its Metal Complexes. *Iran. J. Chem. Chem. Eng.* **2020**, *39*, 105–111.
10. Zheng, J.-W.; Ma, L. Metal complexes of anthranilic acid derivatives: A new class of noncompetitive a-glucosidase inhibitors. *Chin. Chem. Lett.* **2016**, *27*, 627–630. [CrossRef]
11. Oladipupo, O.E.; Ibukun, D.T.; Olalekan, T.E. Synthesis and characterisation of mixed ligand dinuclearmetal(II) complexes of anthranilic acid and pyridine-2-aldoxime. *Niger. J. Chem. Res.* **2018**, *23*, 39–50.
12. El-Roudi, A.M.M.; Aly, A.A.; Abd El-Gaber, A.A.; El-Shabasy, M. Reactivity of Some Transition Metal Complexes of Anthranilic Acid with Leucine and Monochloroacetic Acid. *Croat. Chem. Acta* **1988**, *61*, 775–782.
13. Abdulkarem, L.K.; Mahdi, S.H. Spectroscopic, Structural and Antibacterial Activity of Mixed Ligand Complexes from Schiff Base with Anthranilic Acid. *IOP Conf. Ser. J. Phys. Conf. Ser.* **2019**, *1234*, 012089. [CrossRef]
14. Al-Jorani, K.R.H. Preparation, Characterization of Mixed-Ligand Complexes for Some Divalent Transition Metal Ions Involving Biologically Important Bidentate Ligands. *Am. Sci. Res. J. Eng. Technol. Sci. ASRJETS* **2017**, *38*, 77–89.
15. Doungsoongnuen, S. Synthesis of Copper(II), Nickel(II), Zink(II), Manganese(II) Complexes Mixed Ligand from Sulfonamides of Antranilic Acid and 2,3,4-Aminopyridines. Ph.D. Thesis, Srinakharinwirot University, Bangkok, Thailand, May 2011. Available online: https://ir.swu.ac.th/jspui/bitstream/123456789/381/2/Sutanun_D.pdf (accessed on 1 July 2023).
16. Humphrey, S.M.; Redshaw, C.; Holmes, K.E.; Elsegood, M.R. Acid/amide bonding for anthranilic acid derivatives: Crystal structures of $[W(X)Cl_3(HO_2CC_6H_4NH\text{-}2)]$ (X = O, NPh). *Inorg. Chim. Acta* **2005**, *358*, 222–226. [CrossRef]
17. Ros, T.G.; van Dillen, A.J.; Geus, J.W.; Koningsberger, D.C. Modification of Carbon Nanofibres for the Immobilization of Metal Complexes: A Case Study with Rhodium and Anthranilic Acid. *Chem. Eur. J.* **2002**, *8*, 2868–2878. [CrossRef] [PubMed]
18. Ozkan, S.Z.; Eremeev, I.S.; Karpacheva, G.P.; Bondarenko, G.N. Oxidative Polymerization of N-Phenylanthranilic Acid in the Heterophase System. *Open J. Polym. Chem.* **2013**, *3*, 63–69. [CrossRef]
19. Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. Synthesis of Anthranilic Acid Derivatives through Iron-Catalyzed Ortho Amination of Aromatic Carboxamides with N-Chloroamines. *J. Am. Chem. Soc.* **2014**, *136*, 646–649. [CrossRef] [PubMed]
20. Prasher, P.; Sharma, M. Medicinal chemistry of anthranilic acid derivatives: A mini review. *Drug Dev. Res.* **2021**, *82*, 945–958. [CrossRef] [PubMed]
21. Zheng, C.-M.; Chang, L.-L.; Ying, M.-D.; Cao, J.; He, Q.-J.; Zhu, H.; Yang, B. Aldo–keto reductase AKR1C1–AKR1C4: Functions, regulation, and intervention for anti-cancer therapy. *Front. Pharmacol.* **2017**, *8*, 119. [CrossRef]